Food Chemistry 141 (2013) 1489–1495

Contents lists available at SciVerse ScienceDirect

Food Chemistry

journal homepage: www.elsevier.com/locate/foodchem

Transfer of perfluorooctane sulfonic acid (PFOS) from contaminated feed to dairy milk

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ARTICLE INFO

Article history:
Received 1 October 2012
Received in revised form 4 March 2013
Accepted 11 April 2013
Available online 19 April 2013

Keywords:
PFOS
Toxicokinetic model
Dairy cows

ABSTRACT

Dietary intake is the predominant route for human exposure to perfluorooctane sulfonic acid (PFOS). Single pollution events may thus affect human exposure if polluted ground and water is used to produce animal feed or food. In this study, a physiologically based pharmacokinetic (PBPK-) model is derived that describes the uptake of PFOS from contaminated feed by cows and its subsequent elimination through the cows' milk. Parameter values of the model were estimated by fitting to experimental data of a cow feeding trial. Model calculations showed that almost all PFOS ingested is excreted through the cows' milk. The elimination rate, however, was low as the estimated half-life in the cow was 56 days and it may, thus, take a long time after an initial pollution event to produce PFOS-free milk. The derived model can be used to estimate the transfer of PFOS through the dairy food chain and can be used for comparison of various contamination routes.

1. Introduction

Due to their chemical stability, surface tension lowering properties and ability to create stable foams, perfluoroalkyl and polyfluoroalkyl substances (PFASs) (terminology used as described in Buck et al. (2011)) are widely used for many purposes, such as in coatings, fire-fighting foams and as water repellents in leather, paper and textiles. Application of these compounds started in the early 1950s and continues until today. Due to the widespread use of PFASs, they are globally found in the environment, both in wildlife and in humans, even in remote regions as the Arctic (Giesy & Kannan, 2001). Highest concentrations, however, are found near industrialised regions due to discharge of industrial and municipal wastewater and fire-fighting operations (Prevedouros, Cousins, Buck, & Korzeniowski, 2005).

The most studied compounds within the PFAS group are perfluorooctane sulfonic acid (PFOS) and perfluoroctanoic acid (PFOA). These compounds are persistent in humans and the environment and are the most widely encountered compounds within the PFAS group (Fromme, Tittlemier, Völkel, Wilhelm, & Twardella, 2009). PFOS has recently been designated as a persistent organic pollutant under the Stockholm convention as an Annex B substance (i.e., restricted in its use) (United Nations Environmental Programme, 2009). It is found to cause various toxic effects such as hepatotoxicity, developmental toxicity, immunotoxicity, hormonal effects and carcinogenic potency in animal studies (Fromme et al., 2009). As a result of the widespread presence of PFASs, and due to their toxicological nature, the primary global manufacturer of these compounds stopped production in 2002, which resulted in a decrease in PFAS compounds in human plasma (Olsen et al., 2008).

Human exposure to PFOS and PFOA may occur via household dust, outdoor air, drinking water and food. In general, dietary intake is considered the most important route of human exposure (Cornelis et al., 2012; Domingo, 2012; EFSA, 2012; Haug, Huber, Becher, & Thomsen, 2011). Calculations for European countries showed that exposure to background concentrations results in average dietary intakes of PFOS that are well ng (kg bw day)$^{-1}$ below the Tolerable Daily Intake (TDI) of 150 ng kg^{-1} bw day^{-1} (Clarke et al., 2010; Cornelis et al., 2012; Domingo et al., 2012; EFSA, 2012; Ericson et al., 2008; FSA., 2006; Haug et al., 2010; Noorlander, van Leeuwen, te Biesebeek, Mengelers, & Zeilmaker, 2011).

However, apart from dietary exposure to background levels, humans may also be exposed to PFAS due to single pollution events. Such an event occurred in Germany in 2006, where contaminated field conditioner was used in North Rhine-Westphalia. This resulted in elevated PFAS levels in surface and drinking water in this

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http://dx.doi.org/10.1016/j.foodchem.2013.04.035

area (Skutlarek, Exner, & Farber, 2006). Based on these results, an extensive monitoring programme was started in North Rhine–Westphalia with PFAS measurements in human tissues (Hölzer et al., 2008; Wilhelm et al., 2009), feed, cow milk and fish (Wilhelm, Kraft, Rauchfuss, & Hölzer, 2008). Concentrations found in milk were generally low, which would indicate that localised contamination of pasture grass or feed consumed by farm animals may not be an important route for elevated PFAS exposure in food producing animals (Fromme et al., 2009). However, these results were based on only four samples. Even though milk, generally, contains a low concentration of PFOS, it can be an important contributor to PFOS intake due to the large quantities consumed in some countries. Noorlander et al. (2011) found that 25% of the total PFOS intake was due to milk consumption, whereas beef and fish contributed 21% and 9%, respectively. Therefore, the contamination route from the environment up to consumer milk should be further explored.

Contamination routes throughout the food chain, however, are largely unknown. In order to determine the effect of a single pollution event on the dietary intake of PFOS, it is necessary to quantify the transfer of this compound throughout the food chain. A literature study revealed that most studies focused on the presence of PFOS in water and marine animals, whereas limited data are available for the presence of PFOS in crops and farm animals (van Asselt, Rietra, Römkens, & van der Fels-Klerx, 2011). It would, therefore, be useful to model the uptake of PFOS from feed and its subsequent presence in animal food products. These type of models, i.e. physiologically based pharmacokinetic (PBPK-) models have been developed for rats and monkeys (Andersen, Clewell Iii, Tan, Butenhoff, & Olsen, 2006; Harris & Barton, 2008; Loccisano, Campbell, Andersen, & Clewell, 2011; Loccisano, Campbell, Butenhoff, Andersen, & Clewell, 2012a, 2012b; Tan, Clewell Iii, & Andersen, 2008), but not for farm animals.

The aim of the current study, therefore, was to quantify the transfer of PFOS from feed to animal food products using PBPK modelling. As a case study, we focused on the transfer from contaminated fodder to milk from dairy cows.

2. Material and methods

2.1. Experimental design

Feeding trials were performed at the Federal Institute of Risk Assessment (BfR) using six lactating cows ranging between 2.5 and 5.5 years old with an average body weight of 583 kg. The cows were fed (upload phase) with "naturally" contaminated feed (hay and grass silage), which was harvested from the contaminated region in Lower Saxony, Germany. After 28 days, three cows were slaughtered. The other three cows were fed with non-contaminated feed for a further 21 days (depuration phase), after which they were also slaughtered. During the feeding trial, samples were taken from the milk, blood plasma, urine and the feed. Samples of urine were non-representative because no effort was taken to determine the total daily urinary excretion. After slaughter, tissue samples were collected from the liver, kidney and muscle (*Musculus longissimus dorsi*). Samples were stored in Perfluoroalkyl acids (PFAAs)-free vessels and kept frozen (−20 °C) until analysis. The experimental design is further described in Kowalczyk et al. (2013).

2.2. Chemical analysis

All samples were analysed for the presence of PFOS by the Chemical and Veterinary Analytical Institute Münsterland–Emscher–Lippe. Plasma samples were treated with formic acid/water (1:1) (Kärrman, van Bavel, Järnberg, Hardell, & Lindström, 2004), samples of feed were extracted once with methanol (VDLUFA method). Milk, organ and meat samples were analysed after enzymatic digestion and excretion on an SPE column using lipase and protease as described in Bernsmann and Fürst (2008). Subsequently, separation was performed on an Agilent 1290 SL HPLC system and individual analytes were separated using a Phenomenex Gemini column (3 μm, C18, 100 A, 150 × 2 mm). ^{13}C-labelled PFOS was used as internal standard. The limit of detection (LOD) was defined as the signal to noise ratio of 3:1 of the qualifier ion and quantified against external calibration curves. The limit of quantification (LOQ) was defined as the concentration with relative standard deviation of around 20%. Recoveries of spiked samples ranged between 85% and 110%. The analytical method is further described in Kowalczyk et al. (2013) and Ehlers (2012).

2.3. Modelling transfer

A PBPK-model was developed for transfer of PFOS from feed to milk. The model was developed based on a previously derived model for PFASs in fish (Van Eijkeren, Brandon, & Zeilmaker, 2011) and adapted to reflect the uptake and excretion of PFOS in cows. The final model is illustrated in Fig. 1. The approach used is comparable to other PBPK models (Berntssen et al., 2011; Hoogenboom et al., 2010; Van Eijkeren, Zeilmaker, Kan, Traag, & Hoogenboom, 2006). A fraction (F_{sys}) of the daily dose, D, enters the cow's blood circulation. The amount, A, of PFOS in its unbound form (subscript u) is bound (subscript b) to serum proteins, in particular albumins (Jones, Wenyue, De Coen, Newsted, & Giesy, 2003), with association clearance rate $CL_a = CL_{a,s}V_s$ (L day^{-1}), where $CL_{a,s}$ (day^{-1}) is the specific association clearance per litre serum and V_s is the serum volume. It is assumed that the protein bound formulation is eliminated through clearance to milk: $CL_m = CL_{m,s}V_m$ (L day^{-1}), where $CL_{m,s}$ (day^{-1}) is the specific milk clearance per litre of milk and V_m is the daily milk volume. In concordance with the experimental findings of PFOS in dairy cattle (Kowalczyk et al., 2013), the model depicted in Fig. 1 contained clearance via milk as the predominant elimination route from the animal body. Indeed, preliminary simulation runs revealed that other routes of elimination could not be identified.

The number of transfer flows and partition coefficients in the model was further reduced from six, in the original fish model, to

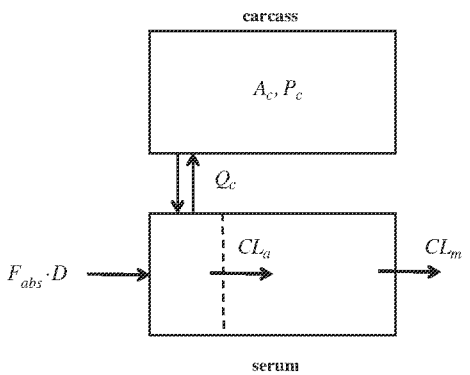

Fig. 1. Model illustration of the carry-over of PFOS from feed to dairy-cows milk. A fraction, F_{sys}, of the daily dose, D, enters the blood circulation. The amount, A, of PFOS in its unbound form (subscript u) is bound (subscript b) to serum proteins, especially albumins, with association clearance rate CL_a. Its protein bound formulation is eliminated through clearance to milk, CL_m, and through other routes of elimination CL_e. Transfer between unbound PFOS in serum and PFOS in carcass is modelled with a transfer flow Q_c (the blood flow to the lumped liver/kidney/muscle compartment) and an equilibrium partition (P_c) of PFOS between serum and carcass.

two in the current model by lumping muscle, liver and kidney tissues to one "carcass" compartment as for these tissues only one sample per cow was available. Transfer between unbound PFOS in serum and carcass is modelled with a transfer flow Q_c (not necessarily blood flow as transfer may be diffusion limited) and an equilibrium partition (P_c) of PFOS between carcass and unbound PFOS in serum. Transfer flow Q_c was estimated as $Q_{c,s}V_s$ (L day^{-1}), where $Q_{c,s}$ is the specific transfer per litre serum. The following differential equations were solved to derive the concentrations of PFOS in serum, milk and carcass:

$$\frac{dA_u}{dt} = F_{sys}D - CL_aC_u - Q_c\left(C_u - \frac{C_c}{P_c}\right) \quad (1)$$

$$\frac{dA_b}{dt} = CL_aC_u - CL_mC_b \quad (2)$$

$$\frac{dA_c}{dt} = Q_c\left(C_u - \frac{C_c}{P_c}\right) \quad (3)$$

$$\frac{dA_m}{dt} = CL_mC_b \quad (4)$$

where A_u, A_b, A_c and A_m (μg) denote the amounts of PFOS as free portion in serum, as bound portion in serum, in carcass and in milk, respectively. Their respective concentrations (C_u, C_b, C_c and C_m) were calculated as the amounts of PFOS divided by their volumes. It was assumed that a dairy-cow's net body weight is 85% of its live weight, including the gastrointestinal content and urine. The liver percentage of net body weight was estimated to be 1.9% and the fraction of kidney weight was assumed to be 0.3%, i.e. about one sixth of the fraction of liver weight, analogous to humans (Derks et al., 1993). The fraction of muscle was assumed to be 35% of the net body weight corresponding to 30% of life body weight (Bergström, 1974; OMAFRA., 2011). Serum volume was assumed to be a fraction of 50% of blood volume that is 9.3% of body weight (Derks et al., 1993). The carcass concentration was determined as the weighted mean of the reported concentrations for muscle, liver and kidney.

Calibration of the model parameters was based on data from the cows that were sacrificed after the depuration phase. Data from cows sacrificed after the upload phase were used for model validation. Parameter fitting was performed by optimising the loglikelihood of parameters with respect to all data on milk, serum and carcass for all three cows simultaneously using ACSL optimise (www.acslx.com).

3. Results

The average daily intake of PFOS during the 28 day feeding period was between 3.1 and 5.6 mg day^{-1} resulting in an average dairy cow's PFOS exposure between 5.3 and 9.6 μg kg^{-1} bw day^{-1}. Concentrations of PFOS in blood, milk and carcass (average of kidney, liver and muscle tissue) were used to derive parameter values for the model (Eq. (1)). This resulted in F_{sys} to have its maximum value of 1. Of the remaining parameters (CL_a, CL_m, Q_c and P_c), the specific milk clearance showed a robust estimate at $CL_{m,s}$ = 0.017 - day^{-1}. The other parameters were calibrated conditionally, i.e. only ratios of parameter values could robustly be estimated. For instance, when the calibrated values of $CL_{a,s}$ = 3.6 day^{-1}, $Q_{c,s}$ = 13.4 - day^{-1} and P_c = 28 were re-used as initial estimation in the fitting procedure, this resulted in values of $CL_{a,s}$ = 120 day^{-1}, $Q_{c,s}$ = 430 - day^{-1} and P_c = 940, thereby identifying the ratios of the parameter values $Q_{c,s}/P_c$ = 0.47 and $P_c/CL_{a,s}$ = 8 (note that this calibration guarantees accurate transfer calculations in the dose range of the modelled experimental study). Parameters were estimated using data for the three cows that were first fed with PFOS contaminated feed and subsequently with PFOS-free feed. Obtained parameter values were further validated using data for the three cows that were slaughtered after the upload phase. Results of the model calibration and validation in the blood samples are depicted in Fig. 2. As can be seen, the model validation confirmed that the established parameter values were capable of describing the PFOS levels found in the blood samples. Results for the milk samples showed a similar pattern (results not shown). Fig. 3 shows the overall results of the model predictions for PFOS concentrations in milk, blood and carcass for the various cows. This figure shows that the concentration in milk and blood continues to increase after exposure has stopped (after 28 days). Carcass concentrations (average of muscle, liver and kidney) show a steady decrease after 28 days.

Model calculations also showed that once steady state is reached, practically all PFOS ingested via feed is excreted via the milk. For a dairy cow of 600 kg, steady state is reached in 4.5, 3 or 2 months given a milk yield of 12.5, 25 or 50 L day^{-1}, respectively (Fig. 4). The corresponding steady state milk concentrations were 240, 120 and 60 μg L^{-1} milk, respectively. When a cow of 600 kg with a milk yield of 25 L day^{-1} is exposed to PFOS-containing feed (3 mg day^{-1}) for 30 days and to PFOS-free feed afterwards, it takes another 30 days to reach the maximum concentration in the milk. Once this maximum is reached, the estimated half-life in milk can be estimated from a log-plot of the milk concentration, resulting in a half-life of around 56 days. This half-life is determined by the transfer of PFOS between carcass and serum. Fig. 5 shows that, in this scenario, PFOS is completely eliminated from the milk after about 1.5 years.

4. Discussion

This study described a PBPK-model for PFOS transfer from contaminated feed to cow's milk. Parameter estimation for the derived model was complicated by the fact that the experimental time of loading and depuration (28 and 21 days, respectively) was short compared to the half-life of PFOS in dairy cows. Furthermore, only three carcass samples (average of liver, kidney and muscle) were available for model calibration. This resulted in uncertainty in the model parameters' estimations as parameter values, except for milk clearance, varied between simulation runs. However, as the model's milk clearance was uniquely identified as well as the ratios of the remaining model parameters, this guarantees accurate transfer calculations up to 10 mg PFOS day^{-1} by cows. The model was, therefore, capable of describing the increasing trend in PFOS concentrations in milk and serum as was also confirmed by the model validation (Fig. 2).

Based on the model, the estimated half-life of PFOS was 56 days, which is longer than the half-life of 9 days for juvenile Rainbow trout (Van Eijkeren et al., 2011) and of around 16 days for chicken (Yeung et al., 2009). However, in other studies on animal species longer half-lives were estimated: for Blackrock fish the estimated half-life was 70 days (Van Eijkeren et al., 2011), for chicken a half-life of 125 days was reported after subcutaneous administration (Yoo et al., 2009), in rats a half-life of 110 days was reported, and in monkeys a half-life of 150 days was established (review from Lau et al. (2007)). For humans, the serum elimination half-life for PFOS was estimated as 4.8 years (Olsen, 2007). Half-lives, however, differ between studies due to inter- and intra-species variations (Trudel et al., 2008), various dose levels (Loccisano et al., 2012a), different ages, and/or different modes of exposure (Trudel et al., 2008; Yeung et al., 2009). Overall, it can be concluded that PFOS elimination is slow in animal species, which was confirmed by the estimated half-life of 56 days in the current study.

PFOS concentrations were shown to increase in plasma and milk during the PFOS-free feeding period in lactating cows. Experiments in monkeys, however, showed a rapid loss of PFOS in blood plasma after PFOS dosing had stopped (Andersen et al., 2006; Tan

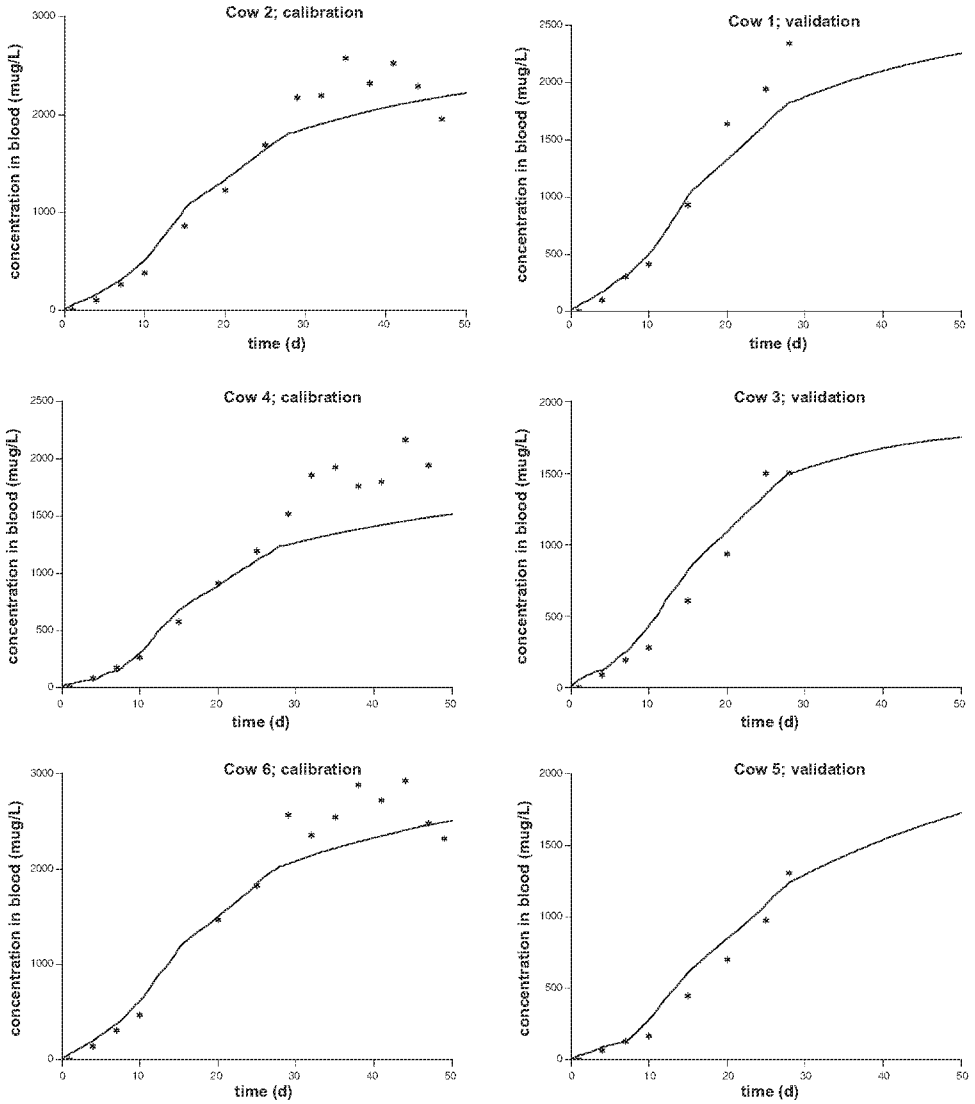

Fig. 2. Time-course of the PFOS concentration in blood serum. The left panels show the comparison of the fitted model to the calibration data (cows slaughtered after the depuration phase). The right panels show the model verification using data from cows that were slaughtered after the upload phase.

et al., 2008). In these experiments the monkeys were fed with contaminated feed for 26 weeks, which is much longer than in the current experiment. It is possible that steady state was reached within these 26 weeks, after which PFOS levels declined in the blood plasma. Experiments in other farm animals, such as sheep, chickens and steer, confirmed the continuous increase of PFOS levels in plasma after dosage had stopped, as found in the current study (Kowalczyk, Ehlers, Fürst, Schafft, & Lahrssen-Wiederholt, 2012; Lupton, Huwe, Smith, Dearfield, & Johnston, 2011; Yeung et al., 2009). Apparently, PFOS has a high accumulation potential and a slow elimination rate (Kowalczyk et al., 2012). In chicken, PFOS first accumulated in the liver, after which it was redistributed into the blood and kidney for elimination from the body (Yeung et al., 2009).

PFOS elimination may occur via faeces, urine and milk or egg production. Sheep experiments showed that after 21 days, elimination of PFOS into milk was 1–2% and 4–5% of the administered dose appeared in the faeces (Kowalczyk et al., 2012). Exposure in steers to a single dose of PFOS showed that PFOS concentrations in urine and faeces were negligible compared to concentrations found in the body, especially in blood plasma (Lupton et al., 2011). Lactating cows are comparable to steers, except for the fact that they have an extra and more efficient excretion route: milk clearance. The current feeding trial showed that milk clearance increased over time up to 24% of daily intake after 28 days of exposure. This illustrates the high milk clearance in cows when compared to sheep, probably resulting from the higher milk yield (roughly 100 times the milk yield in sheep). The dominance of milk clearance over other excretion routes resembles the excretion mechanism in fish. In this species excretion via the gills appeared the most efficient excretion route, the relevance of other elimination routes was negligible (Van Eijkeren et al., 2011). Initial simulations assuming an excretion factor other than through milk were in concordance with this finding.

Model calculations further showed a high correlation between PFOS concentrations in blood serum (as intermediate phase) and milk: after a few days there is an almost constant ratio of concentrations in milk and blood. Such a positive correlation has also been established in humans ($R^2 = 0.7$) (Kärrman et al., 2006) and in the earlier mentioned sheep experiment (Kowalczyk et al., 2012).

The model described in this study is helpful in determining the effect of a pollution event on the uptake and excretion of PFOS by dairy cows, and thus helps to quantify the effect of pollution events

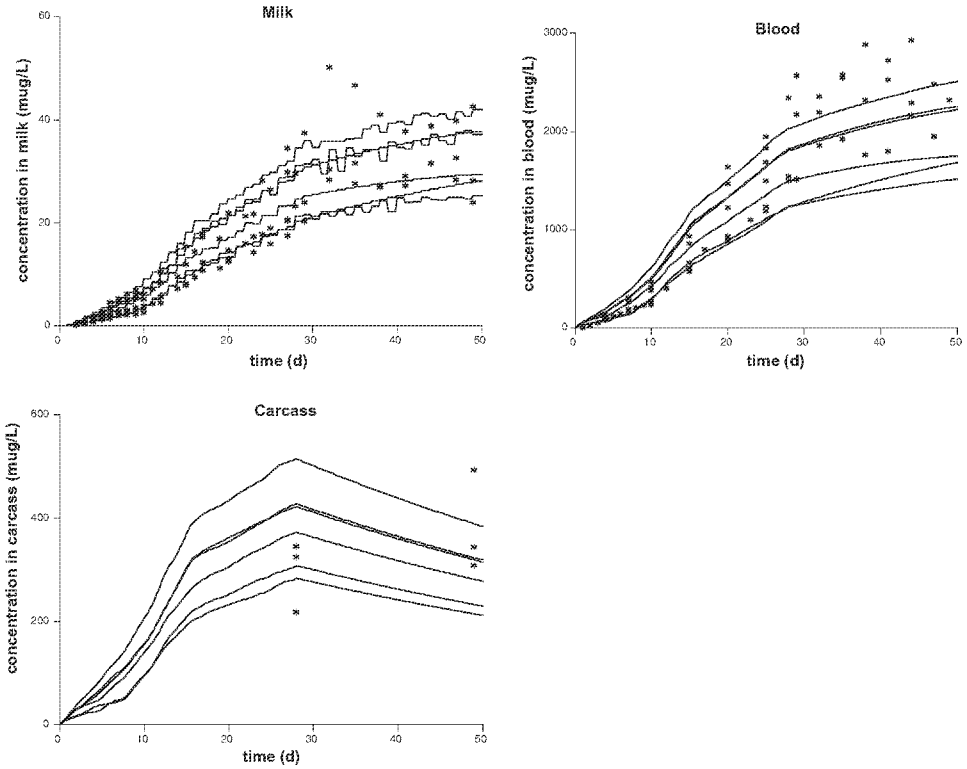

Fig. 3. Model predictions and data on PFOS concentrations in milk, serum and carcass for cows that were fed with contaminated feed for 28 days.

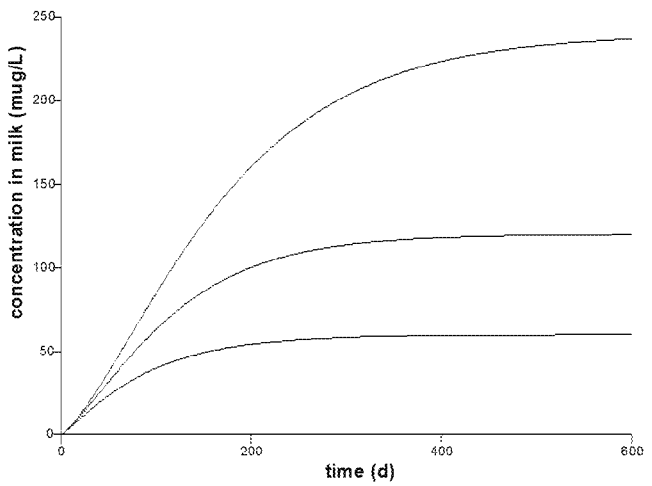

Fig. 4. PFOS concentration in milk as simulated using the PBPK model for an average dairy cow of 600 kg live weight, lactating 12.5 L (upper line), 25 L (line in middle) or 50 L (lower line) per day, that is contaminated through feed with 3000 μg PFOS per day for a period of 600 days.

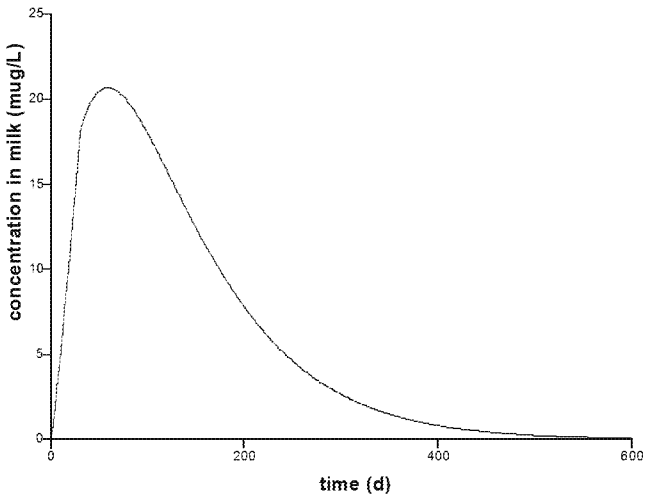

Fig. 5. Model simulation of the time-course of the concentration of PFOS in milk for a cow of 600 kg live weight and milk production of 25 L per day that is contaminated through feed with 3000 μg PFOS per day during 30 days after which contamination is stopped.

on human exposure via dairy milk consumption. It showed that PFOS has a slow elimination rate and it thus takes a long time (depending on the cow's body weight and milk yield) to eliminate PFOS from the milk. EFSA established a TDI of 150 ng (kg bw day)$^{-1}$ (EFSA, 2008), which means a maximum exposure between 750–3000 ng day^{-1} for children between 6 months and 4 years old (5–20 kg). Assuming a daily consumption of 300 mL, the maximum concentration of PFOS in milk for these young children can then be established as ranging between 2.5 and 10 μg L^{-1}. Fig. 5 indicates that these concentrations will be reached when cows are fed with contaminated fodder. Even adults (assuming a body weight of 70 kg and a daily milk consumption of 500 mL) will reach the TDI at the peak of the contamination.

Background concentrations in dairy milk are usually at a low level, around 10 pg g^{-1} in The Netherlands, and exposure to these levels does not result in adverse health effects as the TDI will not be reached (Noorlander et al., 2011). The model calculations in this paper, however, showed that in case of pollution events, PFOS may accumulate in cow's milk to such a level that its consumption may lead to a PFOS intake which equals or exceeds the TDI, particularly in a vulnerable population such as small children.

As only one part of the food chain was quantified (transfer from feed to milk), other parts of the food chain should be quantified in a similar way in order to compare the contribution of the various routes (drinking water, crops, animal products) to human dietary PFOS exposure in pollution events. This will support policy makers in establishing measures to prevent human exposure, such as the application of waiting periods, in case future events should occur.

Acknowledgements

The authors greatly acknowledge the financial contribution from the INTERREG project "Safeguard" and the Dutch Ministry of Economic Affairs. Stefan van Leeuwen (RIKILT, Institute of Food Safety) is thanked for critically reviewing this paper.

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